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AGILENT TECHNOLOGIES, INC.
Legal Department, DL429
Intellectual Property Administration
P.O. Box 7599
Loveland, CO 80537-0599

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte DOUGLAS A. AMORESE, KAREN W. SHANNON, PATRICK J. COLLINS and PAUL K. WOLBER

Appeal 2007-4480
Application 09/870,939
Technology Center 1600

Decided: June 10, 2008

Before ERIC GRIMES, DEMETRA J. MILLS, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to polynucleotide arrays. The Examiner has rejected the claims as obvious and as lacking an adequate written description in the Specification. We have jurisdiction under 35 U.S.C. § 6(b). We reverse the written description rejection but affirm the obviousness rejections.

BACKGROUND

"Arrays of biopolymers, such as arrays of … polynucleotides (such as DNA or RNA), are known and are used, for example, as diagnostic or

screening tools. Such arrays include regions (sometimes referenced as features or spots) of usually different sequence biopolymers arranged in a predetermined configuration on a substrate (the substrate linked biopolymers sometimes being referenced as 'probes')." (Spec. 1.)

The Specification discloses that "arrays made with shorter length biopolymer probes (such as from synthetic sources) … have higher specificity due to the shorter length of the probes … with minimal cross reactivity to related sequences," but that such probes may miss interesting observations because of a lack of sensitivity or because they have been designed to the wrong region of a sample target (*id.* at 3). "On the other hand, arrays made with longer length biopolymer probes … are … more sensitive because the longer length biopolymers are able to form a more stable hybrid to the target molecule," but such "probes may miss interesting observations because of their lack of specificity (for example, a failure to detect expression differences within one member of a family if other members are present and unchanged or cross reactive with a different gene entirely)" (*id.*).

The Specification discloses "an array of biopolymers (for example, polynucleotides such as DNA)" having a first set of multiple features, "each of which has first polynucleotide molecules of at least 400 nucleotides in length" and a second set of features, "each of which has second polynucleotide molecules of no more than 100 nucleotides in length" (*id.* at 4).

DISCUSSION

1. CLAIMS

Claims 1-3, 5-20 and 38-41 are on appeal. Claims 1, 11, 14 and 41 are representative and read as follows:

Claim 1: A polynucleotide array comprising:
(a) a first set of multiple features each of which comprises a single stranded cDNA molecule of at least 400 nucleotides in length; and
(b) a second set of features independent of said first set of features each of which comprises a synthetic single stranded second polynucleotide molecule of no more than 100 nucleotides in length.

Claim 11: A polynucleotide array according to claim 1 wherein at least 70% of a sequence of a second polynucleotide molecule is not contained within a sequence of a cDNA molecule.

Claim 14: A polynucleotide array according to claim 1 wherein the sequence of a second polynucleotide is contained within a cDNA molecule sequence.

Claim 41: A polynucleotide array comprising:
(a) a first set of multiple features each of which comprises a cDNA molecule of at least 400 nucleotides in length; and
(b) a second set of features independent of said first set of features each of which comprises a synthetic polynucleotide molecule comprising a nucleotide sequence that is also present in a single stranded cDNA of the first set of features and is of no more than 100 nucleotides in length.

2. WRITTEN DESCRIPTION

Claims 1-3, 5-14, and 38-41 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking an adequate written description in the Specification, on the basis that "the claimed 'independent' relationship of the feature sets" is not described (Answer 4). The Examiner states that "the recitation of 'independent of said first set of features' was added to the

Independent Claims 1 and 41" but is not supported by the Specification (Ans. 4). The Examiner's position is that the Specification merely describes the features and that the "added language encompasses spatial, structural and compositional (e.g. sequence) independence," but that the Specification does not describe any of these independent relationships (*id.*).

Appellants argue that the amendment of the claims to specify that the second set of features is "independent of said first set of features" was intended "to clarify that the features in the first and second sets of features are spatially distinct" and that "one of skill in the art would reasonably interpret independent features that are on the surface of an array as being spatially distinct from each other" (Reply Br. 4). Appellants further argue that support for the disputed limitation is found in "Fig. 2 of the instant application . . . [which] illustrates features (e.g., features 16a and 16b, referred to in the specification as first and second sets of features, respectively) that are spatially distinct and independent from one another" (*id.* at 4).

The purpose of the written description requirement is to "ensure that the scope of the right to exclude, as set forth in the claims does not overreach the scope of the inventor's contribution to the field as far as described in the patent specification." *Reiffin v. Microsoft Corp.,* 214 F.3d 1342, 1345 (Fed. Cir. 2000). To that end, to satisfy the written description requirement, the inventor "must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). "One shows that one is 'in possession' of *the invention* by

describing *the invention*, with all its claimed limitations." *Lockwood v. American Airlines*, 107 F.3d 1565, 1572 (Fed. Cir. 1997).

We agree with Appellants that the Specification provides adequate descriptive support for the disputed limitation. Fig. 2 of the Specification is reproduced below:

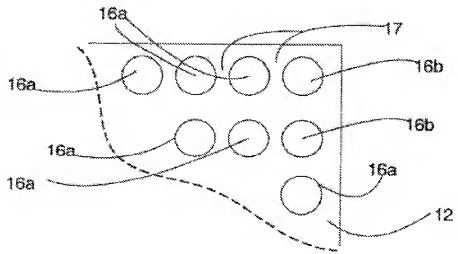

Fig. 2 is said to show an enlarged view of a portion of an array (12) showing multiple features (Specification 6). The Specification discloses that "array 12 is composed primarily of a first set of features 16 (sometimes referenced as 'first features'), with … features 16b of a second set (sometimes referenced as 'second features') positioned at each corner of each array 12" (*id.* at 10). The Specification also discloses that "[e]ach first feature 16a has first polynucleotide molecules of at least 400 nucleotides … in length, while each of the second features 16b has second polynucleotide molecules of no more than 100 nucleotides … in length" (*id.*).

Given that Fig. 2 of the Specification shows that features of a second set (16b) are spatially distinct – and therefore independent – from features of a first set (16a), we conclude that the written description of the invention, as

originally filed, conveys to those of skill in the art that the inventor was in possession of the claimed invention at the time the application was filed.

The rejection of claim 1-3, 5-14, and 38-41 under 35 U.S.C. § 112, first paragraph, for lack of written description in the Specification is reversed.

3. OBVIOUSNESS I

Claims 1-3, 5-10, 14, 38 and 41 stand rejected under 35 U.S.C. § 103 as obvious in view of Bao[1] and Bobrow.[2] Claims 14 and 41 have been argued separately. Claims 2, 3, 5-10, and 38 will stand or fall with claim 1. 37 C.F.R. § 41.37(c)(1)(vii).

The Examiner relies on Bao for disclosing "an array comprising a first set of features having single-stranded polynucleotides of at least 400 nucleotides and a second set of features having single-stranded polynucleotides of about 100 nucleotides" (Office action mailed Aug. 17, 2004 ("Final Rej.") 3). The Examiner finds that "the target elements comprise either genomic DNA, oligomer or cDNA nucleic acids or a mixture of the two" (*id.* at 3). The Examiner further finds that "the combination of different types of nucleic acids on the array … suggests their immobilization to independent features as claimed" and that "arrays comprising combinations of oligonucleotides and cDNAs were well known in the art" as taught by Bobrow (*id.* at 4).

The Examiner concludes that it "would have been obvious to one of ordinary skill in the art … to combine the teachings of Bao et al. and

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[1] Bao et al., US 6,251,601, Jun. 26, 2001.
[2] Bobrow et al., US 6,399,299 B1, Jun. 4, 2002.

Bobrow et al. to provide arrays comprising oligonucleotides and cDNAs as claimed based on the clear suggestion to do so by Bao" (*id.*). The Examiner finds that "one of ordinary skill in the art would have been motivated to provide an array of cDNA fragments of differing lengths (i.e. more than 400bp and less than 100bp) as suggested by Bao … for the expected benefit of analyzing gene expression under optimized conditions as taught by Bao" (*id.*).

We conclude that the Examiner has set forth a prima facie case that claim 1 would have been obvious to the ordinary artisan. Bao discloses "a multi-color, comparative hybridization assay method using an array … for the simultaneous detection of both gene expression and chromosomal abnormalities in a tissue sample" that "employs a comparative hybridization [to the array] of a tissue mRNA or cDNA sample labeled with a first detectable marker, a tissue genomic DNA sample labeled with a second detectable marker, and at least one reference nucleic acid labeled with a third detectable marker" (Bao, col. 2, l. 66 to col. 3, l. 8).

Bao discloses that a "preferred embodiment comprises an array with a mixture of genomic DNA target elements and oligomer DNA or cDNA target elements, with the oligomer DNA/cDNA targets measuring expression and the genomic DNA targets measuring chromosomal change" (*id.* at col. 3, l. 64 to col. 4, l. 2). Bao also discloses that either "a genomic DNA target element and a cDNA target element can each be used in an array format for hybridization to either genomic DNA or expressed gene sequence nucleic acids" (*id.* at col. 6, l. 63 to col. 7, l. 2). Bao also discloses that the "target elements can comprise oligomers, such as those in the range of 8 to about

100 bp, preferably 20 to 80 bp, and more preferably about 40 to about 60 bp" and that cDNAs used as target elements "preferably hav[e] a complexity in the range of about 100 bp to about 5,000 bp" (*id.* at col. 8, ll. 45-48).

We agree with the Examiner that it would have been prima facie obvious to one of skill in the art to arrive at the invention of claim 1 based on the cited prior art. As set forth above, Bao discloses arrays having target elements that detect both gene expression and chromosomal abnormalities. Bao also discloses that a preferred combination is genomic DNA to measure chromosomal change and either oligomers or cDNA to measure gene expression, and that cDNA target elements are interchangeable with genomic DNA target elements for hybridizing to genomic DNA.

Thus, Bao would have made obvious to one of skill in the art an array comprising a combination of cDNA target elements (100 to 5000 nucleotides long) to detect chromosomal abnormalities in genomic DNA and oligomer target elements (preferably 40-60 nucleotides long) to detect gene expression. Although Bao does not expressly suggest that the cDNAs should be more than 400 nucleotides long, its disclosure of an overlapping range of cDNA lengths supports a prima facie case of obviousness. *See In re Geisler*, 116 F.3d 1465, 1469 (Fed. Cir. 1997). In our view, the disclosure of Bobrow is cumulative.

Appellants argue that the rejection is deficient because an array containing both cDNA and synthetic oligonucleotide elements is not suggested by the cited references and because modification of Bao's array to contain both cDNA and synthetic oligonucleotide elements "would render the … array unsatisfactory for its intended purpose" (Appeal Br. 7).

Appellants argue that "Bao's arrays contain either genomic probes and cDNA probes, *or* genomic probes and oligonucleotide probes," but not cDNA probes and oligonucleotide probes (*id.* at 9). Appellants also argue that "Bao does not recognize the use of short genomic probes (less than 20kb) to examine chromosome abnormalities" and that modification of Bao's array to contain cDNAs and oligonucleotides would yield an array that does not contain "genomic probes of the size taught by Bao as necessary," which would be unsatisfactory for Bao's intended use of examining chromosome abnormalities (*id.* at 13).

We do not find this argument to be persuasive. As set forth above, Bao specifically discloses that "a cDNA target element can … be used in an array … for hybridization to either genomic DNA or expressed gene sequence nucleic acids." Thus, although Bao recites that a preferred combination is genomic DNA in combination with either cDNA or oligomer DNA, Bao specifically discloses that cDNA can be used to detect genomic (chromosomal) abnormalities. A person of ordinary skill in the art would have recognized, based on Bao, that an array comprising cDNA target elements and oligonucleotide target elements would be useful in Bao's method of simultaneously measuring gene expression and chromosomal abnormalities.

Appellants further argue that the cited references do not disclose or suggest an array containing oligonucleotide elements and cDNA elements with the size limitations recited in the claims (Appeal Br. 12).

We are not persuaded by this argument. "[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range,

there is a presumption of obviousness. But the presumption will be rebutted if it can be shown: (1) That the prior art taught away from the claimed invention, *In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997); or (2) that there are new and unexpected results relative to the prior art, *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990)." *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004).

As discussed above, Bao discloses that cDNA elements are preferably in the range of about 100 bp to about 5,000 bp and oligonucleotides are preferably in the range of about 8 bp to about 100 bp. Because the claimed ranges overlap with the prior art ranges, the presumption of obviousness applies, and Appellants have not rebutted it.

With regard to claims 14 and 41, Appellants argue that neither Bao nor Bobrow suggests that "certain elements may contain polynucleotides having a sequence that is contained within polynucleotides of other elements" (Appeal Br. 14).

We are not persuaded by this argument. With regard to claim 14, as recognized by the Examiner (Answer 7), the claim language only requires that the array contain a first set cDNA features (at least 400 nucleotides in length) and a second set of independent synthetic polynucleotide features (no more than 100 nucleotides in length), with the second set of polynucleotide features being "contained within a cDNA molecule sequence." Thus, claim 14 only requires that the synthetic polynucleotide sequence is within the sequence of some cDNA, but not necessarily a cDNA of the first set of features recited in claim 1. Thus, given that the synthetic polynucleotides (oligomers) used to detect mRNA expression can be

synthesized based on known cDNA sequences (such as from ESTs), Bao suggests synthetic polynucleotides that are "contained within a cDNA sequence" as specified by claim 14.

The argument is also not persuasive with regard to claim 41. As the Examiner has pointed out (Answer 7), Bao discloses that oligomer DNA targets measure expression and genomic fragments measure a chromosomal region having the same expressed region. Bao teaches that some "forms of cancer are characterized by both over-expression of one or more oncogenes and gene amplification of the chromosomal locus of each oncogene" (Bao, col. 7, ll. 11-14). Bao states that simultaneously testing the same sample for gene expression and chromosomal abnormalities using the disclosed method has the advantage of identifying both the overexpression and its cause, aiding in selection of appropriate therapy (*id.* at col. 7, ll. 17-22).

We agree with the Examiner that Bao's disclosure would have made obvious the product of instant claim 41. Specifically, it would have been obvious to a person of ordinary skill in the art to make an array having features of immobilized cDNAs (to identify chromosomal abnormalities) and oligomers (to assay gene expression), where the sequences of the oligomers are subsequences of the cDNA sequences. Bao would have suggested such an array in its disclosure that simultaneously assaying for gene expression and chromosomal abnormality of the same locus provides advantages in selecting cancer therapy.

4. OBVIOUSNESS II

Claims 11-13, 15-20, and 39-40 stand rejected under 35 U.S.C. § 103 as obvious in view of Bao and CLONTECHniques.[3] Claims 12, 13, 15-20, 39, and 40 have not been argued separately and therefore stand or fall with claim 11. 37 C.F.R. § 41.37(c)(1)(vii).

The Examiner relies on Bao for the disclosure set forth above, but finds that Bao does "not teach the array comprising a second set of features wherein the sequences of the second set of features is not within the first polynucleotide sequence" (Final Rej. 8).

The Examiner relies on CLONTECHniques as disclosing a "similar microarray comprising a second set of polynucleotides wherein the second set comprises control sequences not found in the first set of polynucleotides" (*id.*).

The Examiner concludes that it "would have been obvious to one of ordinary skill in the art … to apply the control probes of Clontech to the kit of Bao … for the expected benefit of providing means for troubleshooting hybridizations as taught by Clontech" (*id.* at 8-9).

We conclude that the Examiner has set forth a prima facie case that claim 11 would have been obvious to the ordinary artisan. Bao is discussed above. CLONTECHniques discloses the use of controls in an array for troubleshooting purposes (CLONTECHniques, legend to Fig. 1 and right-hand col.).

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[3] CLONTECHniques, July 2000, Vol. XV, No. 3, pg. 4, CLONTECH Laboratories, Inc., Palo Alto, CA.

We agree with the Examiner that it would have been prima facie obvious to one of skill in the art to include control polynucleotides, unrelated to the genes of interest, as taught by CLONTECHniques, in Bao's array because such controls were well-known to be useful in validating the experimental results.

Appellants argue that "Bao is deficient for not specifically teaching a polynucleotide array containing independent cDNA probes and oligonucleotide probes" and that the control oligonucleotide probes disclosed by CLONTECHniques do not cure this deficiency (Appeal Br. 15).

We are not persuaded by this argument because, as discussed above, we conclude that the disputed element is suggested by Bao.

SUMMARY

The Examiner's rejection of claims 1-3, 5-20 and 38-41 under 35 U.S.C. § 103 is supported by the preponderance of the evidence of record. We therefore affirm the rejection of claims 1-3, 5-20 and 38-41 under 35 U.S.C. § 103.

We reverse the rejection of claims 1-3, 5-14 and 38-41 under 35 U.S.C. § 112, first paragraph.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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Legal Department, DL429
Intellectual Property Administration
P.O. Box 7599
Loveland, CO 80537-0599